Measuring Disease and Treatment-Related Symptoms and HRQOL Impacts in Patients with High-Risk Non-Muscle Invasive Bladder Cancer (HR-NMIBC) Using the EORTC QLQ-C30 and EORTC NMIBC-24: Qualitative Literature Review and Gap Analysis.

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Objective

This study aimed to summarize evidence regarding both the patient experience of HR-NMIBC and the suitability of EORTC QLQ-C30 and EORTC NMIBC-24 measures for assessing concepts relevant to HR-NMIBC patients.

Summary of findings

The most frequent signs/symptoms reported in the qualitative literature were hematuria, dysuria, urinary urgency/frequency, and pain. Emotional functioning and needing to be close to a toilet were the most frequently reported impacts of NMIBC.

The EORTC QLQ-C30 and EORTC NMIBC-24 generally provide good coverage and measure the key concepts of importance to patients with HR-NMIBC when jointly administered.

Both PROs have overall satisfactory psychometric properties but evidence is lacking or mixed regarding reliability, validity, and definitions of clinically meaningful change in PRO scores specific to a HR-NMIBC patient population.

Conclusions

Both the EORTC QLQ-C30 and EORTC NMIBC-24 are satisfactory instruments to measure concepts important to NMIBC patients, but further research is recommended to address evidence gaps in psychometric properties within the population of interest.

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Presented at ISPOR, Atlanta, GA • May 5-8, 2024

Background or Introduction

- Non-muscle invasive bladder cancer (NMIBC) represents 75% of bladder cancer diagnoses.[1]
- Patients with high-risk NMIBC (HR-NMIBC) have up to an 80% risk of recurrence and up to a 50% risk of progression over 5 years.[2]
- The humanistic burden of HR-NMIBC and current standard of care (i.e., intravesical Bacillus Calmette- Guérin [BCG]) are well-documented, with improvements in patient-reported symptoms and health-related quality of life (HRQoL) representing key markers of the efficacy of treatment in this population.[3]
- There are unique considerations regarding HR-NMIBC in terms of presentation, prognosis, and treatments that ought to be captured in clinical trial endpoints.[4]
- Adequate evidence of content validity and measurement properties within the specific context of use (i.e., clinical trial population) is critical for any patient reported outcome (PRO) measures intended to support treatment benefit claims.[5,6]
- The EORTC QLQ-C30[7] and EORTC NMIBC-24[8] are PRO measures developed to assess symptoms and HRQoL in cancer patients and in those diagnosed with NMIBC, respectively.

Objectives

The objectives of this study were:

- To summarize evidence regarding the patient experience (symptoms and associated impacts) of HR-NMIBC; and
- To assess the content validity and measurement properties of two commonly used PROs in NMIBC clinical trials: EORTC QLQ-C30 and EORTC NMIBC-24.

Methods

Two targeted literature reviews were conducted: a qualitative literature review (Review A) and a critical instrument review and gap analysis (Review B).

Qualitative literature review (Review A)

- A targeted literature search of MEDLINE®, Embase, and PsycInfo® was conducted using Ovid® in October 2022, with supplementary searches conducted on Google Scholar and key conference proceedings.
- Key words and subject headings terms for NMIBC (e.g., "Non muscle invasive bladder cancer"), concepts of interest (e.g., "quality of life") and methodology (e.g., "interviews) were used, and a limit to articles published in the last 10 years was applied.
- The electronic database search yielded 1,542 abstracts, and five abstracts were identified in the supplementary searches.
- Five abstracts met the inclusion criteria (Table 1), and information was extracted from the full text articles.

Table 1. Qualitative targeted literature review eligibility criteria

	Include	Exclude
Publication type	*Journal article, conference abstracts and excerpts*	-
Disease type	*A relevant clinical term is included in the title and/or abstract (e.g. 'NMIBC').*	*Abstract or title does not include a relevant clinical term for NMIBC in the title and/or abstract or only includes mention of muscle-invasive bladder cancer (MIBC).*
Methodology	*Abstract or title explores the patient experience (e.g. symptoms, impacts) of NMIBC.*	*Article does not explore the patient experience of NMIBC.*
Concepts of interest	*Relevant concept of interest is included in the abstract or title (e.g. 'quality of life' or 'hematuria').*	-

Instrument critical review and gap analysis (Review B)

- The instrument critical review focused on literature regarding the development and validation of the EORTC QLQ-C30 and EORTC NMIBC-24 measures, and the psychometric properties of these measures.
- An electronic search using the same databases, supplementary search sources and limits as the qualitative literature search.
- Terms relating to the PRO instruments (e.g., "EORTC QLQ-C30"), methodology (e.g., "validity") and disease (e.g., "non muscle invasive bladder cancer").
- The electronic search yielded 163 abstracts, and six abstracts were identified through supplementary searches.
- A total of **eleven articles** containing quantitative data relating to the measurement properties of the EORTC QLQ-C30 and EORTC NMIBC-24 mentioning NMIBC were included in this review.
- The EORTC QLQ-C30 and EORTC NMIBC-24 were critically reviewed to identify any potential evidence gaps (see Table 2).

Table 2. Aspects reviewed for each PRO instrument

Aspect assessed	How it was assessed
Conceptual coverage	The concepts assessed by each instrument were cross tabulated with the concepts identified in the qualitative review, to highlight gaps in conceptual coverage and identify any missing concepts.
Face and content validity	Whether instruments captured relevant concepts and appropriateness of instrument for context of use, including identifiable strengths and weaknesses.
Measurement properties	• Item level analyses • Reliability • Construct validity • Interpretation and clinical significance of changes/differences
Prior use	A review of cross-cultural validity and prior use was conducted.

Results

Qualitative literature review (Review A)

Characteristics of literature

- **Figure 1** characterizes the by publication type, methodology, risk status of the sample and experience with BCG.
- The sample size of the studies ranged between 7 and 32 participants, and the time frame of data collection ranged between 2011 and 2021 (unspecified in two studies).
- Overall, qualitative evidence relevant to the **specific context** of use was **limited** (n=5).

Figure 1. Characteristics of reviewed full text articles

Patient experience of NMIBC

- The most frequent signs/symptoms reported in the qualitative literature were **hematuria,**[9-12] **dysuria**,[9-13] **urinary urgency** and **frequency**,[10-13] and **pain**[11] (Figure 2).
- Urinary problems and other symptoms (e.g., pain) were mostly attributed to side effects of BCG therapy in the literature rather than being a symptom of NMIBC (excluding '*hematuria*').

Figure 2. Key signs and symptoms of NMIBC

Hematuria *Reported in n=5 publications*	Dysuria *Reported in n=5 publications*	Urinary urgency and frequency *Reported in n=5 publications*	Pain *Reported in n=2 publications*
Blood in urine is one of the primary symptoms of NMIBC – and the **most of frequently reported symptom** in the qualitative literature.	Discomfort or burning sensation with urination was described as a symptom of NMIBC but also as a side-effect of BCG treatment.	Patients mentioned experiencing the urge to urinate after receiving treatment.	Non-urinatory pain (e.g., in the abdominal area). Less frequently mentioned as a symptom of HR-NMIBC than urinary problems.
Changes in appearance or consistency of patients' urine	Pain, stinging or burning during urination	Both associated with NMIBC treatment, transient medication side effects	Discomfort, aches and pain were experienced in the bladder, pelvic and abdominal area.
Transient medication side effect	Transient medication side effect (pain lasted from 2–3 days to weeks)	"I (…) noticed a sudden urgency to wee"	Discomfort in the genital area or when sitting
"I decided to wait [to urinate] till I got home, ran upstairs and (…) suddenly lots of blood	Catheter or stent adverse event	"I'm now getting up to 3, 4, or 5 times a night this is no longer very pleasant"	
	Described as if "a barbed wire had been pulled through the urethra"		

Impacts on HRQoL

- **Impacts on emotional functioning**[10-13] were the most frequently mentioned impact concepts, specifically: uncertainty about the disease and treatment duration, anxiety, depression and fear of disease recurrence, and death. These were largely attributed linked to fear of death and cystectomy and unrelated to HR-NMIBC specific symptoms.

> "In the last few weeks my resolve has weakened massively. Utterly depressed, feeling like nowhere in my body is safe"[10]

  - Shock at receiving initial diagnosis of NMIBC and worry/anxiety (e.g., concern about possibility of cystectomy, repeated treatment, the NMIBC spreading or getting worse) were reported.
- **Frequent urination and urination** urgency emerged as the **most burdensome** impacts on the daily life and social functioning of NMIBC patients. In particular, **needing to be close to a toilet**[10-13] was the most burdensome impact of HR-NMIBC.

> "My life started to focus on the bathroom. Where is the bathroom? How close is the bathroom? Can I get to the bathroom?"[10]

  - Having to be aware of the location of the closest toilet, needing to plan activities around whether a toilet was available and feeling limited or restricted because of incontinence and other urinary problems emerged in the literature as daily life impacts.
- Mixed impacts were found on **work**[10]: treatment disrupts ability to work, but some patients mentioned an improved work-life balance and re-assessment of priorities.
  - Patients reported absenteeism due to treatment schedule, treatment side effects and emotional impact, as well as inability to work or having to reduce amount of time in work.
- Patients tended to attribute the **impacts on work** and **physical functioning** to the aftermath of treatment rather than to HR-NMIBC symptoms.
- There was some evidence of treatment affecting **mobility and movement**,[10,11] which impacted patients' ability to exercise.

Critical instrument review and gap analysis (Review B)

- Table 3 characterizes the articles in terms of study type, country, sample size, time frame of data collection, cancer type and experience with BCG.

Table 3. Characteristics of reviewed full text articles (Review B)

PRO	Study	Type of study	Country	Sample size	Time frame	Cancer type	BCG experience
EORTC QLQ-C30	Aaronson et al., 1993	Validation, Prospective	Multi-country (incl. US)	305	NS	Lung cancer	NA
	Cocks et al., 2023	Validation, Qualitative	Multi-country (incl. US)	113	2016 - 2020	Multi-cancer	NA
	Yu et al., 2019	Cross-sectional	UK	1160	2005 - 2011	Bladder cancer (76.7% NMIBC)	NS
	Wei et al., 2014	Prospective	CN	106	NS	NMIBC (70.0% IR, 30.0% HR)	NS
	Singer et al., 2013	Cross-sectional	DE	823	2005 – 2011	Bladder cancer (26% NMIBC)	NS
	Gontero et al., 2013	Prospective	IT, DE, US	88	2006 – 2010	NMIBC, IR	Yes (n=59), No (n=61)
	Koga et al., 2010	Prospective	JP	84	2002 - 2005	NMIBC, HR	No
EORTC QLQ-NMIBC24	Blazeby et al., 2014	Validation, Prospective	UK	410	2012	NMIBC (25.4% IR, 74.6% HR)	Yes
	Park et al., 2018	Validation, Prospective	KR	249	2014-2015	NMIBC, risk status NS	Yes (n=49), No (n=127)
	Jung et al., 2020	Cross-sectional	US	398	NS	NMIBC, risk status NS.	NS
	Ripping et al., 2021	Validation, Cross-sectional	NL	1463	NS	NMIBC, LR (n=99), intermediate (n=250) and high risk (n=1,114)	Yes (n=870), No (n=593).

Note. CN: China. DE: Germany. HR: High risk. IR: Intermediate risk. IT: Italy. JP: Japan. KR: South Korea. LR: Low risk. NA: Not applicable. NL: The Netherlands. NS: Not specified. UK: United Kingdom. US: United States

- Evidence for the EORTC QLQ-C30 and EORTC NMIBC-24 face and content validity are detailed in **Table 4**.
- Findings from the instrument review (measurement properties) are detailed in **Table 5**, as per regulatory guidelines for COA development and validation.[6,14,15]
- Findings from a conceptual mapping exercise are detailed in **Table 6**, whereby conceptual coverage is illustrated by mapping items against the concepts identified in the qualitative literature review (Search A).

Table 4. Face and content validity of the EORTC QLC-C30 and EORTC NMIBC-24

Summary of face validity assessment *(for both PROs)*	• Item wording and instructions are clear, unambiguous and patient-friendly. • Response options are clearly worded, adequately distinct, and appropriately ordered. • Appropriate recall period applied to most items across PROs. • Scoring rules and method are clearly described in PRO manuals.
Summary of content validity evidence identified	• **EORTC QLC-C30:** Good content validity described in localized-to-advanced cancer samples in USA and Europe.[16] • **EORTC NMIBC-24:** Interviews with NMIBC patients conducted for the Korean version to assess understanding.[17]

Table 5. Psychometric properties of the EORTC QLQ-C30 and EORTC NMIBC-24

Name of PRO	Psychometric properties: Construct validity	Response distributions	Reliability	Ability to detect change
EORTC QLQ-C30	✓ Multi-trait scaling analyses support the hypothesized scale structure in a sample of lung cancer patients.[7] ? Differences between NMIBC and MIBC patients, but not of high magnitude.[11] ? The role functioning scale showed consistent problems.[7] ? Differences in scores in NMIBC patients with different disease stages not in the expected direction.[23]	✓ No floor nor ceiling effects. Response distributions of different scales followed expected pre and post-treatment patterns.[7] ? HRQoL among NMIBC patients at baseline was relatively high, with mean values for all domains reported as <69 or higher and several symptom domains exceeding 0.9.[23]	? Internal reliability coefficients (Cronbach's alpha) for the multi-item scales were .54-.86 before treatment and .52-.89 during treatment in lung cancer patients. The Role scale had the poorest internal consistency.[7] *NE* No evidence of test-retest reliability in a NMIBC or HR-NMIBC population.	✓ Decreases in global health status and several scales scores after treatment observed with NMIBC patients in the UK[7] and China.[18] ✓ Increased HRQoL over time for NMIBC patients.[13] ✓ Physical function decreased after treatment in intermediate risk NIMBC patients.[20] ? No significant differences in global HRQL and significant improvement in Emotional function in Japanese HR-NMIBC patients following BCG induction/ maintenance.[22] *NE* No evidence of meaningful within-person change or between-group differences in a NMIBC or HR-NMIBC population
EORTC NMIBC-24	✓ Structure confirmed in Dutch and Danish validation studies.[13,24] ✓ Evidence of discriminant validity between most EORTC NMIBC-24 and EORTC QLQ-C30 scales across UK,[8] Korean[17] and Dutch[24] versions. ? Some evidence of known-groups validity in NMIBC population (not specifically HR-NMIBC) and results variable.[8,13,24]	? Ceiling effects in several scales found in the UK,[8] Korean,[17] Dutch,[24] and Danish[13] validation studies.	✓ In the Dutch version test-retest was acceptable for six scales and fair to moderate for three scales. Test–retest reliability was the lowest for malaise.[24] ✓ Good internal consistency for most scales in UK,[8] Korea,[17] Dutch[24] and Danish[13] validation studies.	? Mixed findings of responsiveness across different scales, e.g., little change detected in urinary symptoms in the UK study,[8] whereas Korean study[17] detected significant improvement. *NE* No evidence of interpretation of change identified.
Key	✓ = adequate evidence identified, ? = evidence identified is mixed or inconclusive, *NE* = no evidence identified in this review			

Table 6. Conceptual coverage of the EORTC QLQ-C30 and the EORTC NMIBC-24

	Concept identified in the patient-focused literature	Coverage (Scale: Item) EORTC QLQ-C30	EORTC NMIBC-24	Combined
Symptoms/ treatment # side-effects	Hematuria	No coverage	No coverage	✗
	Urinary urgency*	No coverage	Urinary symptoms: **Item 33**	✓
	Dysuria*	No coverage	Urinary symptoms: **Item 37**	✓
	Frequent urination*	No coverage	Urinary symptoms: **Item 31 & Item 32**	✓
	Flu-like symptoms*	No coverage	Malaise: **Item 38 & 39**	✓
	Pain	Pain: **Item 9**	No coverage	✓
Impacts of NMIBC/ treatment	Emotional/psychological well-being			
	Worry/Anxiety	Emotional: **Item 21, 22**	Future worries: **Items 41-44**	✓
	Low mood/Depression	Emotional: **Item 24**	No coverage	✓
	Shock at initial diagnosis	No coverage	No coverage	✗
	Fear	Emotional: **Items 21, 22**	Future worries: **Item 41-44**	✓
	Concern about possibility of cystectomy	No coverage	No coverage	✗
	Daily activities			
	Restrictions in daily life activity due to needing to be close to the toilet*	Role: **Items 6, 7**	Urinary symptoms: **Item 35**	✓
	Work			
	Absenteeism/reduction in work time*	Role: **Item 6**	No coverage	✓
	Physical functioning			
	Mobility/movement affected*	Physical: **Items 1-4**	No coverage	✓
	Social activities			
	Restrictions/inability in social functioning*	Social: **Item 27**	Urinary symptoms: **Item 35**	✓
	Sleep			
	Disturbed sleep due to increased frequency of night-time urination*	Insomnia: **Item 11**	Urinary symptoms: **Item 34**	✓
	Sexual life impacts			
	Interest/ability (such as getting or maintaining an erection) in sexual activity*	No coverage	Sexual functioning: **Item 47-54**	✓

*Potential overlap between NMIBC symptoms and BCG side-effects

Darker green shading: Direct coverage; (i.e., the item explicitly assesses the concept in its wording)

Lighter green shading: Partial coverage. (i.e., the item does not contain the concept in its wording but assesses a related/similar concept so the response to the concept in question may be reasonably inferred).

No coverage

Key Findings and Conclusions

- The EORTC QLQ-C30 and EORTC NMIBC-24 generally provide good coverage and measurement of the key concepts of importance to patients with HR-NMIBC when jointly administered, except '*hematuria*', '*shock at initial diagnosis*' and '*concerns about the possibility of cystectomy*', which are not captured by either instrument.
- Evidence generally supports the measurement properties of the EORTC QLC-C30 and EORTC NMIBC-24 among patients with NMIBC.
- EORTC QLQ-C30 provides satisfactory conceptual coverage of the most frequently reported impacts of NMIBC by patients in the qualitative literature.
  - While QLC-C30 provides minimal coverage of the urinary symptoms identified in the literature review, these may instead be captured by the EORTC NMIBC-24 which may typically be administered in conjunction with the EORTC QLQ-C30.
- While commonly used measures in oncology, evidence of content validity for EORTC QLC-C30 with respect to a (HR-) NMIBC populations is limited.

Considerations

- Further evidence generation is required to establish reliability, validity and definitions of clinically meaningful change in PRO scores specific to patients with HR-NMIBC.
- The qualitative evidence base regarding NMIBC was relatively scarce (with some publications not having a full-text available) at the time of review, especially for HR-NMIBC.
  - The publications that included HR patients typically did not disaggregate results by risk group.
  - Future patient-centered research is recommended to further characterize the patient experience of (HR-) NMIBC.
- The symptoms and impacts of NMIBC reported by patients in the qualitative literature appear to be mostly attributed to BCG side-effects rather than NMIBC, with further research needed to fully disentangle the burden of treatment from burden of disease.
- '*Hematuria*' is not covered by either instrument, however, this concept may be assessed using biological tests and is not typically targeted by anti-cancer therapies. Incidence may also be confounded with the safety profile of treatments (e.g., BCG).
- In contrast, '*concerns about cystectomy*' are a relevant concept for patients with HR-NMIBC and existing NMIBC HRQoL instruments could be modified to include items covering this disease impact.